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Review

Overview of vasopressor and inotropic agents

ISO and Dobutamine

Yasemin Hacanlı
Department of Cardiovascular Surgery, Faculty of Medicine, Harran University, Şanlıurfa, Turkey

Abstract

Hypotension can often occur during and following anesthesia and surgery. Studies emphasize that end-organ ischemia during surgery is associated with morbidity, hypotension and mortality. Vasoactive agents and fluid volumes are often preferred to improve hypotension during surgery. Despite the widespread use of vasoactive agents, neither the substance nor the dose has been fully defined. Vasoactive agents are divided into two groups according to their functions: vasopressors and inotropes. These agents are believed to regulate end-organ perfusion. But, it also has side effects such as hyperlactataemia, tachycardia, tachyarrhythmias, ischemia and hyperglycemia. The likelihood and severity of these side effects depend on the agent used, its amount and duration. Our aim in this compilation is; To provide an overview of inotropic agents. To give information about ISO and dobutamine, which are inotropic agents, and to briefly touch upon their use in animal studies.

Keywords

Vasoactive Agents, Vasopressor, Inotropic Agents, Isoproterenol, Dobutamine

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Corresponding Author: Yasemin Hacanlı, Department of Cardiovascular Surgery, Faculty of Medicine, Harran University, Şanlıurfa, Turkey.
E-mail: yaseminhacan@hotmail.com P: +90 506 700 27 00
Corresponding Author ORCID ID: https://orcid.org/0000-0002-4427-8149

Introduction

Although the quality of care after surgical procedures has improved, the possibility of postoperative mortality and complications remains a serious threat [1]. Hypotension can often occur during and following anesthesia and surgery. Studies emphasize that end-organ ischemia during surgery is associated with morbidity, hypotension and mortality [2]. Vasoactive agents and fluid volumes are often preferred to improve hypotension during surgery [3]. Despite the widespread use of vasoactive agents, neither the substance nor the dose has been fully defined [4]. Vasoactive agents are divided into two groups according to their functions: vasopressors and inotropes [5]. These agents are believed to regulate end-organ perfusion [6]. Vasopressors act through the adrenergic system and increase blood pressure through vasoconstriction [5]. However, the volume of myocardial oxygen does not increase. This leads to reduced cardiac and systemic perfusion, leading to multiple organ failure and death due to cardiac arrest [7]. Inotropes act by increasing cardiac contractility [5]. The study on inotropes showed that their short-term use provided a neutral effect, while their long-term use led to adverse outcomes in patients hospitalized with acute HF [8]. For this reason, the use of most inotropic agents [especially phosphodiesterase (PDE) and catecholamines (Endogenous: Adrenaline, Noradrenaline, Dopamine and exogenous: Dobutamine, Isoproterenol, Phenylephrine, Milrinone) [9]] is not preferred unless there is hypoperfusion or hypotension [10].

It is possible to list hyperlactatemia, tachycardia, tachyarrhythmias, ischemia and hyperglycemia among the side effects of vasopressors and inotropes [11]. The likelihood and severity of these side effects vary depending on the agent used, its amount, and duration [12].

Isoproterenol (ISO)

Isoproterenol (ISO) is a cardiac β1 and β2 adrenoreceptor agonist with positive chronotropic and inotropic effects [13]. It is a synthetic catecholamine [14]. It has been shown to be successful in activating pulmonary veins, including in highly sedated patients, as well as extrapulmonary veins that trigger atrial fibrillation [13]. However, it plays a role in the synthesis of free radicals by triggering lipid peroxidation. This situation creates critical levels of oxidative stress in the myocardium, leading to infarction-like necrosis in the heart muscle and ultimately irreversible damage to the myocardial membrane [14]. It can lead to cardiac hypertrophy and myocardial apoptosis. The myocardial damage method created by ISO is preferred in examining the protective effect of many drugs on the heart, as it is similar to the pathological changes in heart tissue in the development of human heart failure [15].

Dobutamine

Dobutamine is a β-1 adrenergic agonist [17]. As a result of the fact that cardiomyocytes and inflammatories affect each other, the contractility of the heart decreases. In this case, dobutamine supplementation is preferred to increase cardiac output [18]. Dobutamine directly triggers β1 and α1 receptors, with poor affinity for β2 receptors [19]. In the myocardium, β-1 activates adrenergic receptors. and increases cardiac contractility. MoreoverIn doing so, it does so this without generating tachycardia and vasoconstriction [17]. At doses as lower as than <5 microgram/kilogram/minute (μg/kg/min), dobutamine can cause agonist and antagonist triggering of α1 receptors and vasodilation. However, at doses above >15 μg/kg/min, it may cause vasoconstriction [19]. The half-life of dobutamine is <2 minutes. The benefit depends on the dose-response relationship. The infusion administered in high doses should be used with caution as it may cause the formation of tachycardia [9]. While dobutamine is beneficial in the regulation of heart failure treatment in the short term, it has been explained that it may have the opposite effect in the long term [20].

The hemodynamic effects and adrenergic properties of ISO and dobutamine are briefly summarized in Table 1 [21].

Discussion

Today, various studies are being carried out to investigate the effects of cardiovascular diseases (CVD) on the diagnosis and treatment. In these studies, especially in experimental studies on animals, cardiac injury models were created by using various inotropic agents, methods, surgical techniques and drugs. Our aim is to touch upon some of the experimental daemage models of ISO and dobutamine on animals. ISO, a beta- adrenergic agonist, may play a role in the formation of necrosis similar to myocardial infarction (MI) in rats. This damage is thought

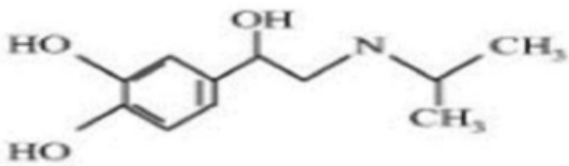

Figure 1. Chemical Structure of ISO [16]

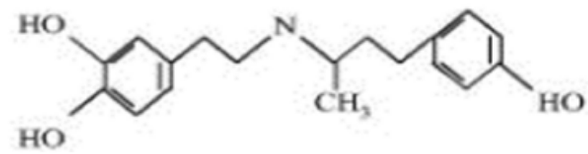

Figure 2. Chemical Structure of Dobutamine [16]

Table 1. For ISO and Dobutamine, Receptors, Dosage administration, Indications and Side Effects [21]

Drug	α1	β1	β2	DA	Dose	C. Indication	Side Effects
Dobutamine	+	+++++	+++	N/A	2.0 to 20 μg · kg^{-1} · min^{-1} (max 40 μg · kg^{-1} ·min^{-1})	Decompensated HF, cardiogenic shock, sepsis-induced myocardial dysfunction, Symptomatic bradycardia unresponsive to atropine or pacing	VA, Tachycardia Cardiac ischemia Hypertension Nonselective beta blocker hypotension
Isoproterenol	0	+++++	+++++	N/A	2 to 10 μg/min	Bradyarrhythmias Brugada syndrome	VA, Cardiac ischemia Hypertension Hypotension

* + through +++++, minimal to maximal relative receptor affinity; 0, zero significant receptor affinity; α1, α-1 receptor; β1, β-1 receptor; β2, β-2 receptor; DA, dopamine receptors: HF, chronic heart failure; N/A, not applicable; C. Indication, Clinical Indication; VA. Ventricular arrhythmias.

to be similar to human myocardial differentiation [22]. In ISO-generated injury models, various biochemical parameters such as lactate dehydrogenase (LDH), creatine phosphokinase-MB (CK-MB) and aspartate transaminase (AST) are evaluated as well as the heart tissue structure to detect damage [23].

In their study, Fan et al. looked at AST, lactate dehydrogenase (LDH), CK and CK-MB levels in plasma to determine the detection of myocardial damage by ISO in male Sprague Dawley rats, and these parameters were higher in the ISO group [24]. Xing et al. induced MI by ISO in rats. When pathological changes in heart tissue in the ISO group were examined compared to the control group, myocardial necrosis and edema, infiltration of inflammatory cells and membrane damage were detected [25]. Another study examined ISO-induced MI damage in rats and found that ISO led to the production of oxidative free radicals that cause irreversible disruption of the cardiac myocyte membrane and myocardial cell death, leading to leakage of markers of heart damage [26]. Yang et al. injected the mice with ISO for two days. After this administration, serum cardiac troponinT (cTnT), CK-MB and LDH content increased and cardiac dysfunction was observed [27]. In another experimental study on rats, an increase in heart weight, heart-to-body weight ratio, malondialdehyde levels in heart tissue and serum, and TNF-a, IL-1β and IL-6 levels in heart tissue homogenates was observed in the ISO group compared to the control group. Decreases in superoxide dismutase and catalase levels have been reported [28].

Dobutamine is a β-1 adrenergic agonist [17]. As a result of the fact that cardiomyocytes and inflammatories affect each other, the contractility of the heart decreases. In this case, dobutamine supplementation is preferred to increase cardiac output [18]. While dobutamine is beneficial in the regulation of heart failure treatment in the short term, it has been explained that it may have the opposite effect in the long term [20]. Azuero et al. administered increasing doses of dobutamine to the piglets' hearts [2.5–15 μg/kg (microgram/kilogram) body weight (min) dobutamine per minute (min), 0.007–0.044 μmol/kg/min (micromol/kilogram/min]. As a result of the application, an increase in left ventricular end-diastolic pressure, heart rate and lactate production was observed. Tissue acylcarnitine levels were higher in the dobutamine group than in the saline group [29]. In their study on dogs, Yi et al. administered low doses (0.01 μg/kg/min) and high doses (0.06 μg/kg/min) to the right coronary artery (RCA) for 15 minutes of hypoperfusion. While low-dose dobutamine administration showed positive results in hypoperfusion-infused right ventricular (RV) myocardial contractile function and cellular energy recovery, the same was not true for high-dose. Therefore, it is important to pay attention to the dosage application [30]. In the experimental study on rats, the rats were loaded with caffeine and dobutamine. Early ventricular contractions were reported in 7 of 8 rats and bidirectional ventricular tachycardia in 6 of 8 rats [31]. Kelm et al. gave rats a stress test with dobutamine. They measured LAD coronary artery velocity before and 72 hours after IR surgery. LAD coronary artery velocity before surgery was higher after dobutamine infusion [32]. In our previous study, we administered dobutamine IP (intraperitoneal) at 40 μg/mouse/day for 15 days to damage mouse hearts. To detect myocardial damage, troponin-I value was checked in addition to electrocardiography (ECG) images. The Troponin-I value was measured to be high in the dobutamine group. In addition, in the histopathological examination of the heart tissue, it was observed that the areas of necrosis in the myocytes were higher in the dobutamine group. Thus, our injury modeling was determined both biochemically and histopathologically [33].

Conclusion

Inotropes increase cardiac output by increasing cardiac contractility with their different functions. However, they show vasoconstrictive or vasodilative activations, which may vary depending on the substance used and the amount given. They have also been among the causes of increased short- and long-term deaths due to common side effects and unnecessary use. If attention is paid to approaches such as identifying the right patient and choosing the right inotrope, inotropes can be utilized in the best way [34].

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and Human Rights Statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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